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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,080	06/19/2003	John L. Magnani	400068.413	7045

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,080	MAGNANI ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/13/04, 1/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The receipt of Information Disclosure Statements filed on 1/13/04, 1/26/04, 6/1/04, and 6/27/05 is acknowledged.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-20 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for a conjugate of the instant compounds of claim 17 with compounds 1-15 in Figure 1, it does not reasonably provide enablement for conjugates with any therapeutic agent as broadly claimed in instant claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(A) The nature of the invention.

(B) State of the art.

(C) Breadth of claims.

(D) The level of one of ordinary skill in the art.

(E) The amount of direction provided by the inventor.

(F) The existence of working examples.

(G) The level of predictability in the art.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The claimed invention relates to a composition comprising a glycomimetic and a diagnostic or therapeutic agent, which is an antineoplastic agent. This encompasses any neoplastic agent. Given the great diversity between various antineoplastic compounds (e.g. alkalating agents, antimetabolite agents, antineoplastic antibiotics, asparaginase, elsar, cytotoxic drugs, floxuridine, lomustine, alkeran, procarbazine,.....etc.), will interfere with the predictability as will be shown later.

The state of the art: The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The closest art suggest the use of the category of glycomimetics combined with an anti-neoplastic agent (Liu et al. US 2002/0128225). The disclosure is not sufficient to

guide a skilled artisan in achieving the present endeavor of conjugating the specific compounds disclosed in instant Figure1 to an anti-neoplastic or diagnostic agent.

The breadth of the claims: The recitation in claim 17, namely a conjugate of a therapeutic or diagnostic agent linked to one compound selected from the 15 structures disclosed in figure 1 is a broad recitation. The terms therapeutic or diagnostic are seen merely as a functional language. The terms therapeutic or diagnostic agent is also seen to reasonably include not only known compounds but also unknown compounds as of the filing date.

The level of one of ordinary skill in the art: The level of skill of those in this art is that of one having experience in organic synthesis is very high. The amount of direction provided by the inventor in the instant case for the terms "therapeutic or diagnostic" are purely a functional distinction that reads on any known or unknown compound that might have the recited functions. The specification (pages 12) recites broad categories of compounds for potential therapeutic agents. The claims also should include written description of an invention, which requires a precise definition, such as by structural formula or chemical name, of the claimed subject matter sufficient to distinguish it from other materials. One skilled in the art therefore cannot visualize or recognize the identity of the members of the genus.

The existence of working examples: The working examples set forth in the instant specification are drawn to synthesis of the compounds of the structures recited in instant claim 17. One of ordinary skill in the art will not extrapolate this to other

conjugates since the examples provided are not representative of the therapeutic agents or conjugates encompassed by the recitation of instant claim 17.

The level of Predictability in the Art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427.2d 833, 166 USPQ (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one of skill in the art cannot fully visualize or recognize the identity of the members of the genus. In the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the conjugates herein. Goodman and Gillman 's, "Pharmacological Basis of Therapeutics l0th edition. 1996 page 54", teaches that the frequency of significant beneficial or adverse drug interactions is unknown (bottom of the left column at page 54). Relatively small changes in the drug level can have significant adverse consequences. In the instant case one of skill in the art would not be able to fully predict possible adverse drug to drug interactions occurring with the many combinations of any compounds having the functional properties in the pharmaceutical conjugates claimed herein. Thus, the teachings of Goodman and Gillman clearly support that the instantly claimed invention is highly unpredictable.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the information set forth, the instant

disclosure is not seen to be sufficient to represent all the conjugates encompassed by the recitation of the instant claims. One of ordinary skill in the art would have to carry out undue experimentation to practice the instant invention. Since any structural variation to a compound would be reasonably expected to alter its properties, one of ordinary skill in the art would be required to perform undue experimentation to determine which, if any, of the compounds "therapeutic agents" would be useful to make a conjugate with the compounds recited in instant claim 17.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The compounds 1-15 referred to in the claim need to be incorporated in the body of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thoma et al. WO 9806730 "Thoma" in view of Liu et al. US 2002/0128225.

Thoma teaches glycomimetics, derivatives of sialyl-Lewis X and A, in which the natural neuraminic acid residue and the natural N-acetylglucosamine monomer are replaced. Thoma teaches that under the influence of cytokines, the endothelium, which lines the blood vessels, expresses adhesion proteins on its surface. The P and E selectins bring about by a protein-carbohydrate interaction with glycolipids and glycoproteins on the leukocyte membrane, the so called "rolling" of leukocytes. The leukocytes are slowed down by this process, and there is activation of certain proteins (integrins) on their surface, which ensure firm adhesion of the leukocytes to the endothelium. This is followed by migration of the leukocytes into the damaged tissue. There are many situations in which the recruitment of leukocytes by adhesion to the endothelial cells is abnormal and in excess resulting in tissue damage instead of repair. This is the case in disorders such as metastatic cancer (abstract and page 1). Accordingly, Thoma's compounds are similar to the present application compounds (for example, see

preparation 2 page 47 in relation with Figure1 compound 1 of the instant application), and the compounds are suggested to treat cancer.

Thoma did not disclose the conjugation of anti-neoplastic drugs with the glycomimetic compounds.

Liu discloses methods for delivering polysaccharides by a pulmonary route to achieve local and systemic therapeutic effects. Liu also discloses that polysaccharides have a diverse array of therapeutic utilities like glycomimetics, and that glycomimetics have been used for treatment of inflammation, cancer and other immunologic disorders [0109]. Liu suggested that antineoplastic drugs can be conjugated to the glycomimetic like Fluorouracil [0127]. In addition, Liu teaches that a label, such as a radioactive or fluorescent label can be attached to the polysaccharide and used to determine the distribution of inhaled polysaccharide [0070], this disclosure reads on the diagnostic conjugations, which the compounds may target. Furthermore Liu suggested the use of the glycomimetics as an angiogenesis promoting agents (claim 20, and 35), and also as an inhibiting agent as in case of vascular condition, which is selected from the group consisting of neovascular disorders of the eye, osteoporosis, psoriasis, and arthritis (claims 30, and 31).

Note that Liu teaches that the methods taught herein are sometimes described with reference to heparin-like glycosaminoglycans (HLGAGs) but the properties taught herein can be extended to other polysaccharides, and unless a claim specifies otherwise the claims encompass any polysaccharides having a therapeutic utility [0074]

Accordingly, it would have been obvious to one skilled in the art at the time the invention was made to expand the teaching of Thoma that the glycomimetics prepared in his invention can be used to treat neoplasms and combine it with the teaching of Liu who suggested that a glycomimetic can be conjugated with fluorouracil to enhance its potency against cancers and metastasis of cancers.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5, and 6 of copending Application No. 10/742,631 ('631). Although the conflicting claims are not identical, they are not patentably distinct from each other because: Instant claim 17 is drawn to a conjugate comprising a therapeutic agent linked to the compounds according to Figure

1 and 5 of '631 is drawn to the conjugate of similar compounds and a therapeutic agent for *pseudomonas* bacteria therapy.

Claim 17 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 10 of copending Application No. 10/992,238 ('238). Although the conflicting claims are not identical, they are not patentably distinct from each other because: Instant claim 17 is drawn to a conjugate comprising a therapeutic agent linked to a compound according to Figure 1 and claim 10 of '238 recites the conjugation of similar compounds with a therapeutic or diagnostic agents.

Claim 17 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 10/992,480 ('480). Although the conflicting claims are not identical, they are not patentably distinct from each other because: Instant claim 17 is drawn to a conjugate comprising a therapeutic agent linked to a compound according to Figure 1 and claim 6 of '480 recite the same combination.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nabila Ebrahim 8/1/06

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER